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# Accepted Manuscript

## Review

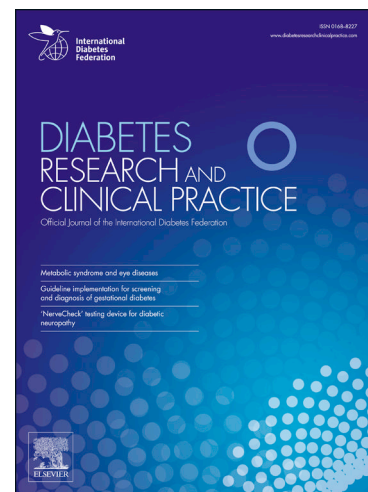
Are glucose profiles well-controlled within the targets recommended by the International Diabetes Federation in type 2 diabetes? A meta-analysis of results from continuous glucose monitoring based studies

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**Full title:** Are glucose profiles well-controlled within the targets recommended by the International Diabetes Federation in type 2 diabetes? A meta-analysis of results from continuous glucose monitoring based studies.

**A running head:**

Intra-day glucose control in type 2 diabetes

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## Abstract

*Aims:* To assess continuous glucose monitoring (CGM) derived intra-day glucose profiles using global guideline for type 2 diabetes recommended by the International Diabetes Federation (IDF).

*Methods:* The Cochrane Library, MEDLINE, PubMed, CINAHL and Science Direct were searched to identify observational studies reporting intra-day glucose profiles using CGM in people with type 2 diabetes on any anti-diabetes agents. Overall and subgroup analyses were conducted to summarise mean differences between reported glucose profiles (fasting glucose, pre-meal glucose, postprandial glucose and post-meal glucose spike/excursion) and the IDF targets.

*Results:* Twelve observational studies totalling 731 people were included. Pooled fasting glucose (0.81 mmol/L, 95% CI, 0.53–1.09 mmol/L), postprandial glucose after breakfast (1.63 mmol/L, 95% CI, 0.79–2.48 mmol/L) and post-breakfast glucose spike (1.05 mmol/L, 95% CI, 0.13–1.96 mmol/L) were significantly higher than the IDF targets. Pre-lunch glucose, pre-dinner glucose and postprandial glucose after lunch and dinner were above the IDF targets but not significantly. Subgroup analysis showed significantly higher fasting glucose and postprandial glucose after breakfast in all groups: HbA1c <7% and  $\geq$ 7% (53 mmol/mol) and duration of diabetes <10 years and  $\geq$ 10 years.

*Conclusions:* Independent of HbA1c, fasting glucose and postprandial glucose after breakfast are not well-controlled in type 2 diabetes.

Word count: 200/200

**Keywords:** Continuous glucose monitoring, Glucose, Glucose profiles, Type 2 diabetes

## 1. Introduction

One of the main therapeutic goals of type 2 diabetes management is to achieve and maintain glucose within target range and to prevent diabetes related complications [1]. The clinical gold standard for assessing glycaemic control is currently HbA1c [2]. A target HbA1c (glycated haemoglobin) of <7% (53 mmol/mol) is recommended for people with type 2 diabetes to reduce the risk of developing complications [1]. However, HbA1c provides only an average assessment of glycaemic control [3], and intra-day glucose profiles: fasting glucose, pre-meal glucose and postprandial glucose; need to be well-controlled as these glucose profiles impact on HbA1c [4]. Recently the introduction of continuous glucose monitoring (CGM) technology enables detailed and accurate assessment of glucose profiles throughout the day [5]. The International Diabetes Federation (IDF) have produced evidence-based global guideline for type 2 diabetes which recommend targets of fasting or pre-meal glucose  $\leq 6.5$  mmol/L and postprandial glucose  $\leq 9$  mmol/L respectively to achieve recommended HbA1c <7% (53 mmol/mol) [1]. The aim of this meta-analysis is to pool evidence from observational studies using CGM to ascertain if glucose profiles are well-controlled within the IDF range throughout the day in type 2 diabetes.

## 2. Material and methods

### 2.1. Protocol and registration

A protocol for this review and meta-analysis was developed and is available from PROSPERO (PROSPERO 2016: CRD42016049207).

### 2.2. Search strategy

The Cochrane Library, MEDLINE, PubMed, CINAHL and Science Direct databases were searched for literature published in English until March 2018. The following three main search terms and their synonyms were used: (I) type 2 diabetes and its synonyms (e.g. non-

insulin dependent diabetes mellitus and adult onset diabetes); (II) continuous glucose monitoring (CGM) and its synonyms (e.g. CGM and real-time CGM) and (III) glucose and its synonyms (e.g. glycaemic variability and postprandial glucose).

### 2.3. Selection of studies and eligibility criteria

In this systematic review and meta-analysis, studies investigating fasting glucose, pre-meal glucose and postprandial glucose using CGM in people with type 2 diabetes until March 2018 were included. The study designs eligible for this review were different types of observational studies (e.g. cross-sectional study, case control study and prospective study) which included people with type 2 diabetes aged over 18 years. No restrictions were placed on types of CGM and whether participants took anti-diabetes agents or on the type of anti-diabetes agents. Experimental studies (drug and exercise interventions), qualitative studies and any studies in people with type 1 diabetes, people with latent autoimmune diabetes in adults, people with gestational diabetes, pregnant people and critically ill people were excluded.

Two reviewers (ACP and SFMC) carried out three phases to select studies. These two reviewers reviewed articles independently, but they discussed and decided together in case of doubt. In phase one, the titles of articles were screened, and the relevant articles were selected for phase two. In phase two abstracts were reviewed, and in phase three the full texts of the remaining articles were reviewed.

### 2.4. Data extraction

The information was extracted from the eligible articles on: (1) general information (including main author and the year of publication), (2) characteristics of studies (including study design and duration), (3) characteristics of sample (including age, sample size, medications and duration of type 2 diabetes) and (4) outcome measures (including fasting

glucose, pre-meal glucose, postprandial glucose and HbA1c). Two reviewers (ACP and SFMC) performed data extraction independently, and any discrepancies were resolved by discussion with the input of a third reviewer (AFK) where needed.

## 2.5. Data synthesis and analysis

For primary outcome measures, mean differences between CGM measured fasting glucose, pre-meal glucose and postprandial glucose and the IDF targets (Fasting glucose  $\leq 6.5$  mmol/L, Pre-meal glucose  $\leq 6.5$  mmol/L, Postprandial glucose  $\leq 9$  mmol/L) were meta-analysed using the inverse variance method. To evaluate postprandial glucose excursion, post-breakfast glucose spike, post-lunch glucose spike and post-dinner glucose spike were calculated by subtracting pre-meal glucose from post-meal glucose. Difference between the IDF targets for pre-meal glucose (6.5 mmol/L) and postprandial glucose (9 mmol/L) was defined as target post-meal glucose spike ( $\leq 2.5$  mmol/L). Mean differences between post-breakfast glucose spike, post-lunch glucose spike and post-dinner glucose spike and the IDF target ( $\leq 2.5$  mmol/L) were also meta-analysed. The standard errors used in meta-analysis were calculated from standard deviations [6–14] and interquartile ranges [4] for each study [15–17]. The standard errors for the IDF target values were substituted with zero [18]. The  $I^2$  statistic was used to assess the heterogeneity between studies [19], and the random effects model was used for moderate to high heterogeneity [20,21]. To ascertain if glucose profiles are well-controlled in people with below and above target HbA1c, we stratified the results for the following subgroups: HbA1c  $< 7\%$  (53 mmol/mol) and HbA1c  $\geq 7\%$  (53 mmol/mol). Finally, because diabetes duration can influence intra-day glucose profiles, we also stratified results for duration of diabetes  $< 10$  years and duration of diabetes  $\geq 10$  years. Statistical analyses were performed using the Cochrane Review Manager 5.3. The mean difference and 95% confidence interval (CI) are reported in meta-analysis, and P-value  $\leq 0.05$  was considered statistically significant. By assuming a Gaussian distribution between subjects, the

percentages of people with poor fasting glucose ( $>6.5$  mmol/L), pre-meal glucose ( $>6.5$  mmol/L), postprandial glucose ( $>9$  mmol/L) and HbA1c ( $\geq 7\%$  or 53 mmol/mol) were also estimated.

## 2.6. Quality assessment

The quality of all studies was assessed using the QUALSYST checklist from “Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields” (Alberta Heritage Foundation for Medical Research) [22]. To interpret the quality of studies, an arbitrary quality score was set at 70% of the possible total score of 100%, and the study with score  $\geq 70\%$  was graded as high-quality. Two reviewers (ACP and SFMC) conducted the quality assessment of articles independently with discrepancies resolved through discussion.

## 3. Results

### 3.1. Literature search and study selection

The primary searches identified 2745 articles via the Cochrane Library, MEDLINE, PubMed, CINAHL and Science Direct databases. After duplicates were removed, 1624 articles remained at the title and abstract review phases. After titles and abstracts were reviewed, 1540 articles were excluded for the following reasons: irrelevant ( $n = 1353$ ), type 1 or other diabetes ( $n = 95$ ), pregnant people ( $n = 10$ ), critically ill people ( $n = 45$ ), qualitative study ( $n = 1$ ), experimental studies ( $n = 26$ ) and age under 18 years ( $n = 10$ ). Full-text of 84 articles were reviewed using predefined inclusion and exclusion criteria, and 12 articles meeting the inclusion criteria were included in this systematic review and meta-analysis (Fig. 1).

### 3.2. Study characteristics

Twelve observational (eight cross-sectional, two longitudinal, one prospective and one retrospective) studies investigating fasting glucose, pre-meal glucose and postprandial



glucose by CGM were included. Participants with known type 2 diabetes for 1.7 years [4], 4.6 years [11], 6.9 years [9], 7.3 years [12], 8.1 years [15], 11 years [7], 12.9 years [6] and 14.7 years [10] were respectively used in eight studies. One study included newly diagnosed type 2 diabetes [8], and three studies did not report the sample's duration of diabetes [13,14,16]. Characteristics and main findings of the studies are reported in Table 1.

Five studies were performed in Europe (1 in Germany, 1 in the UK, 1 in the Netherlands, 1 in the UK and France and 1 in Denmark). Four studies were conducted in Asia (3 in Japan and 1 in Taiwan), and one was from Australia and the remaining two were from Iran. The sample size and study duration ranged from  $n = 11$  [15] to  $n = 248$  [16] and 1 day [4,6] to 12 days [7], respectively. Total 731 people from twelve observational studies were included in this meta-analysis, and fasting glucose, pre-breakfast glucose, pre-dinner glucose, postprandial glucose after breakfast, postprandial glucose after lunch, postprandial glucose after dinner and HbA1c data were respectively obtained from 619, 410, 410, 645, 476, 476 and 731 people. Participants were taking different anti-diabetes agents (metformin, sulphonylurea, thiazolidinedione,  $\alpha$ -glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, sodium-glucose cotransporter 2 inhibitor, glinides and insulin) [6–13,15,16]. Participants with diet management were included in four studies [4,12,14,16].

The study objectives stated were to evaluate glucose profiles [4–10,13,15,16] and associations of HbA1c with glucose profiles [11,12,14]. Fasting glucose (pre-breakfast glucose) in ten studies [4,7–11,13–16] and pre-lunch and pre-dinner glucose in four studies [4,8,11,16] were reported. Nine studies reported postprandial glucose after breakfast [4,6–10,12,13,16], and seven studies reported postprandial glucose after lunch and dinner [4,6–9,13,16]. Participants were asked to record time of meals in nine studies [7–13,15,16] and were instructed to consume meals at standardised time in two studies [4,6]. The glucose values before corresponding meals were regarded as fasting glucose (pre-breakfast glucose),

pre-lunch glucose and pre-dinner glucose [4,7–11,13–16]. Postprandial glucose was defined as average 2 h glucose [6,7,9,13] and peak glucose after meal [4,8,10,12,16]. All studies measured and reported HbA1c using laboratory analyses.

### 3.3. Quality of studies

The majority of studies had high quality scores, ranging from 70% [9] to 94% [8,12]. All studies sufficiently expressed study designs and methods, but with no clear information of participants' medications in one study [6].

### 3.4. Accuracy of CGM used in studies

Accuracy of CGM was determined by mean absolute relative difference (MARD). Medtronic CGMS system Gold (2<sup>nd</sup> generation) or Medtronic MiniMed CGM in nine studies [4,6,7,9,11–14,16], Medtronic iPro2 CGM in three studies [8,10,11] and GlucoDay S CGM in one study [15] were used, and their MARD values were 11%-20.6%, 9.9% and 15%, respectively [13,23–27].

### 3.5. Overall analyses of glucose profiles

Poor fasting glucose, pre-lunch glucose, pre-dinner glucose, postprandial glucose after breakfast, postprandial glucose after lunch, postprandial glucose after dinner and HbA1c control were observed in 100%, 92.7%, 32.2%, 96.7%, 72.3%, 72.3% and 67.0% of people, respectively. Fig. 2A-C show the meta-analysis forest plots of mean differences in fasting glucose, pre-lunch glucose and pre-dinner glucose compared with the IDF target. Fasting glucose was significantly higher than the IDF target (0.81 mmol/L, 95% CI, 0.53–1.09 mmol/L,  $P < 0.00001$ ). But, there were no significant differences between pre-lunch glucose (0.21 mmol/L, 95% CI, -0.06–0.49 mmol/L,  $P = 0.12$ ) and pre-dinner glucose (0.24 mmol/L, 95% CI, -0.40 to 0.87 mmol/L,  $P = 0.47$ ) and the IDF target.

Mean differences between postprandial glucose after meals and post-meal glucose spikes and the IDF targets are described in Fig. 3A-F. Compared with the IDF target, postprandial glucose after breakfast was significantly higher (1.63 mmol/L, 95% CI, 0.79–2.48 mmol/L,  $P = 0.0002$ ). However, postprandial glucose after lunch (0.38 mmol/L, 95% CI, -0.33–1.08 mmol/L,  $P = 0.29$ ) and dinner (0.45 mmol/L, 95% CI, -0.37–1.26 mmol/L,  $P = 0.28$ ) were not significantly different from the IDF target. Post-breakfast glucose spike (1.05 mmol/L, 95% CI, 0.13–1.96 mmol/L,  $P = 0.02$ ) was significantly higher than the IDF target but not post-lunch glucose spike (0.35 mmol/L, 95% CI, -0.62–1.32 mmol/L,  $P = 0.48$ ) and post-dinner glucose spike (0.80 mmol/L, 95% CI, -0.29–1.88 mmol/L,  $P = 0.15$ ).

### 3.6. Subgroup analyses of glucose profiles

Subgroup analyses of glucose profiles show that fasting glucose was significantly higher than the IDF target in both HbA1c <7% (53 mmol/mol) (0.68 mmol/L, 95% CI, 0.39–0.97 mmol/L,  $P < 0.00001$ ) and HbA1c  $\geq$ 7% groups (53 mmol/mol) (0.94 mmol/L, 95% CI, 0.37–1.50 mmol/L,  $P = 0.001$ ) (Table 2). Moreover, significantly high postprandial glucose after breakfast was observed in both HbA1c <7% (53 mmol/mol) (0.67 mmol/L, 95% CI, 0.13–1.20 mmol/L,  $P = 0.01$ ) and HbA1c  $\geq$ 7% groups (53 mmol/mol) (2.79 mmol/L, 95% CI, 1.88–3.70 mmol/L,  $P < 0.00001$ ). Post-breakfast glucose spike was significantly higher than the IDF target in HbA1c  $\geq$ 7% group (2.29 mmol/L, 95% CI, 1.40–3.18 mmol/L,  $P < 0.00001$ ), but there were no significant differences between the remaining glucose profiles and the IDF targets in both groups.

Both groups with duration of diabetes <10 years (1.06 mmol/L, 95% CI, 0.39–1.72 mmol/L,  $P = 0.002$ ) (1.37 mmol/L, 95% CI, 0.50–2.23 mmol/L,  $P = 0.002$ ) and duration of diabetes  $\geq$ 10 years (0.80 mmol/L, 95% CI, 0.45–1.15 mmol/L,  $P < 0.00001$ ) (2.22 mmol/L, 95% CI, 0.41–4.03 mmol/L,  $P = 0.02$ ) had significantly higher fasting glucose and postprandial glucose after breakfast compared with the IDF targets (Table 2). There was significantly high

post-breakfast glucose spike in group with duration of diabetes <10 years (1.26 mmol/L, 95% CI, 0.15–2.38 mmol/L,  $P = 0.03$ ) but not in group with duration of diabetes  $\geq 10$  years (1.04 mmol/L, 95% CI, -2.68–4.77 mmol/L,  $P = 0.58$ ) compared with the IDF target. Both post-lunch glucose spike and post-dinner glucose spike in group with duration of diabetes <10 years were not significantly different from the IDF target. Differences between pre-lunch glucose, pre-dinner glucose, postprandial glucose after lunch and postprandial glucose after dinner and the IDF targets were not significant in both groups.

#### 4. Discussion

CGM technology enables continuous accurate monitoring of intra-day glucose profiles. To our knowledge, this is the first systematic review and meta-analysis that synthesise new knowledge about intra-day glucose profiles acquired by this technology and assessed using the IDF targets. We found that people with type 2 diabetes do not achieve the IDF targets for fasting glucose, postprandial glucose after breakfast and post-breakfast glucose spike with diet management and anti-diabetes agents. Pre-lunch glucose, pre-dinner glucose, postprandial glucose after lunch, postprandial glucose after dinner, post-lunch glucose spike and post-dinner glucose spike are marginally higher than the IDF targets but not statistically significant.

Subgroup analyses revealed that this poor control of fasting glucose and postprandial glucose after breakfast was independent of HbA1c and duration of diabetes, because even people with HbA1c <7% (53 mmol/mol) and duration of diabetes <10 years experienced poor glucose control before and after breakfast. It appears that postprandial glucose after breakfast was higher in people with HbA1c  $\geq 7\%$  (53 mmol/mol) and duration of diabetes  $\geq 10$  years than those with HbA1c <7% (53 mmol/mol) and duration of diabetes <10 years, and this is in agreement with previous epidemiological evidence [4,28]. Postprandial glucose after lunch,

postprandial glucose after dinner and post-breakfast glucose spike seems to achieve the IDF targets in people with HbA1c <7% (53 mmol/mol), but all glucose profiles were above the targets in people with HbA1c  $\geq$ 7% (53 mmol/mol) and duration of diabetes <10 years and  $\geq$ 10 years.

There is strong observational evidence that fasting glucose is associated with vascular events and mortality, and HbA1c level is consistently influenced by fasting glucose or pre-breakfast glucose and pre-lunch glucose but not with pre-dinner glucose [4,8,14,29,30,31,32]. High postprandial glucose after breakfast and lunch can also predict the cardiovascular events in type 2 diabetes, and this effect is independent and stronger than fasting glucose and HbA1c [33,34]. In general, the association of HbA1c with postprandial glucose was well established [4,35,36] but not with postprandial glucose after each meal in a day. A study identified a higher correlation of HbA1c with postprandial glucose after breakfast than postprandial glucose after lunch and no effect of postprandial glucose after dinner in type 2 diabetes [8]. Although this evidence is limited, high glucose profiles after breakfast seems to be clinically important. The finding from this meta-analysis suggests that people with type 2 diabetes with HbA1c <7% (53 mmol/mol) or  $\geq$ 7% (53 mmol/mol) are very likely to have high fasting glucose and postprandial glucose after breakfast, and this might be clinically useful to improve diabetes management.

An important point of this review is that there is the need for the improvement of current diabetes management, and other adjunct therapy should be added. One potential therapeutic target is to modify lifestyle factors, in particular, sedentary/sitting time, leading to high glucose profiles in people with type 2 diabetes. The negative impact of daily sedentary/sitting time and the beneficial effect of interruption of sedentary/sitting time on fasting glucose and postprandial glucose were observed in recent cross-sectional studies [37–39]. However, these studies only looked at the association of sedentary pattern and periodic venous glucose before

and after a test meal rather than continuous glucose profiles throughout the day in free-living settings. Future studies are therefore needed to evaluate the impact of daily sedentary behaviour, physical activity pattern and other lifestyle factors on intra-day glucose profiles using CGM.

There are several strengths of this meta-analysis. First, the quality scores of the included studies are relatively high. Second, subgroup analysis used in this meta-analysis allowed us to evaluate glucose profiles for HbA1c <7% (53 mmol/mol), HbA1c  $\geq$ 7% (53 mmol/mol), duration of diabetes <10 years and duration of diabetes  $\geq$ 10 years. Third, the use of CGM in the included studies allowed us to analyse and evaluate the full picture of glucose profiles throughout the day. Finally, the IDF guideline used in the present meta-analysis is evidence-based and specific for type 2 diabetes, and 36% of national guidelines used globally were based on the IDF guideline [40].

This meta-analysis also has some limitations. First, the sample size was relatively small in most of the studies included in this meta-analysis, and this tends to be the case in CGM based studies due to the relatively high cost of CGM. Second, there might be study selection bias because the majority of studies included in this meta-analysis are cross-sectional and the availability of other study designs are limited. Third, the reliability of pooled glucose profiles might be limited by the heterogeneity between studies, and this may result from variability in study designs, methodologies, participants and anti-diabetes agents between studies. Nonetheless, the random effects model allowing the study outcomes to vary in a normal distribution between studies was used to conduct analyses [41]. Fourth, some important glucose control measures, such as glycaemic variability and bedtime glucose, were not reported in this meta-analysis, and these glucose control measures should be evaluated in future studies. Fifth, CGM used in the studies were much outdated, and insights into glucose profiles were limited because their monitoring duration (e.g. GlucoDay S CGM monitors

glucose for 2 days) was relatively short compared to current CGM systems (e.g. FreeStyle Libre CGM monitors glucose for 14 days). Finally, the use of different CGM with different MARD values in the included studies might influence pooled glucose profiles and might contribute to the observed heterogeneity.

In conclusion, fasting glucose and postprandial glucose after breakfast do not achieve the IDF targets in type 2 diabetes even with currently prescribed diet management, anti-diabetes agents and HbA1c <7% (53 mmol/mol). People with type 2 diabetes are therefore at risk of diabetes complications, and adjunct therapy such as lifestyle modifications should be promoted. The impact of lifestyle factors on intra-day glucose profiles using current CGM should be explored in future studies.

Word count: 4039

### **Author contribution**

ACP, AFK and SFMC conceived this study and contributed to the study design. ACP produced the study question, conducted data collection and analysis, interpreted the results, drafted and revised the manuscript. SFMC contributed to study question, data collection and analysis. AFK, AC, TK and SFMC contributed to the revision of the manuscript. The final manuscript was approved by all authors.

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The views, results, discussions and conclusions are those of the authors. The funding agencies did not play any role in preparing and writing up review and making a decision to submit manuscript.

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**Conflict of interest disclosures**

No potential conflicts of interest associated with this article were reported.

**Prior presentation**

Parts of this review in abstract form were presented at Diabetes UK Professional Conference, Manchester, United Kingdom, 8-10 March 2017.



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Tables

Author (year)	Study design	Study duration (days)	Sample size	Age (years)	Medications	Fasting glucose (mmol/L)	PPG after breakfast (mmol/L)	Pre-lunch glucose (mmol/L)	PPG after lunch (mmol/L)	Pre-dinner glucose (mmol/L)	PPG after dinner (mmol/L)	HbA1c (%)	HbA1c (mmol/mol)
Ando et al. (2013) [4]	Cross-sectional	1	30	42-66	Diet	6.9 ± 0.3	11.9 ± 0.7	6.5 ± 0.3	11.7 ± 0.7	6.4 ± 0.4	12.4 ± 0.8	7.7 ± 0.2	61 ± 1.2
Cichosz et al. (2013) [8]	Cross-sectional	3	86	61 ± 1.1	Met	6.9 ± 0.1	10.2 ± 0.3	6.6 ± 0.1	8.4 ± 0.2	6.6 ± 0.2	8.8 ± 0.2	6.5 ± 0.1	48 ± 0.4
Monnier et al. (2013) [16]	Cross-sectional	3	248	59.9 ± 0.6	Met, SU, $\alpha$ -GI, TZD, DPP-4 I, Diet	6.9 ± 0.1	11.1 ± 0.2	6.6 ± 0.1	9.3 ± 0.1	6.3 ± 0.1	9.3 ± 0.1	7.2 ± 0.1	55 ± 0.6
Hay et al. (2003) [7]	Longitudinal	12	25	73.9 ± 0.9	Met, SU	7.7 ± 0.4	9.3 ± 0.6		8.7 ± 0.6		8.2 ± 0.5	6.2 ± 0.2	44 ± 1.2
Bonakdaran and Khajeh-Dalouie (2011) [9]	Longitudinal	6	17	42.4 ± 2.1	Met, SU	7.7 ± 0.4	10.7 ± 0.8		9.9 ± 0.5		9.5 ± 0.7	6.3 ± 0.4	45 ± 2.5
Yano et al. (2013) [6]	Cross-sectional	1	49	67.3 ± 1.5	ADA		11.6 ± 0.5		11.1 ± 0.7		11.6 ± 0.5	8.7 ± 0.2	72 ± 1.2
McGeoch et al. (2012) [14]	Cross-sectional	3	29	62 ± 1.1	Diet	7.3 ± 0.2						6.7 ± 0.1	50 ± 1.2
Praet et al. (2006) [15]	Cross-sectional	2	11	58 ± 1	Met, SU	8.6 ± 0.6						7.4 ± 0.3	57 ± 1.9
Takeishi et al. (2016) [10]	Retrospective	4	106	66.6 ± 1.1	Met, SU, $\alpha$ -GI, TZD, DPP-4 I, GLP-1 RA, Rapid acting insulin secretagogue, SGLT2 I, Insulin	7.2 ± 0.2	12.6 ± 0.3					8.7 ± 0.1	71 ± 1.5
Lin et al. (2016) [11]	Cross-sectional	3	46	54.2 ± 1.5	Met	8.1 ± 0.2		7.5 ± 0.3		7.6 ± 0.2		7.5 ± 0.1	58 ± 0.1
Kohnert et al. (2007) [12]	Prospective	4	63	62.9 ± 1.1	Diet, Met, SU, Insulin		9.5 ± 0.2					6.1 ± 0.1	43 ± 0.4
Bonakdaran and Rajabian (2009) [13]	Cross-sectional	3	21	51.9 ± 2.1	Met, SU, Meglitinides	7 ± 0.2	8.7 ± 0.6		7.9 ± 0.3		7.5 ± 0.3	6.7 ± 0.1	50 ± 0.6

Abbreviation: Met, metformin; SU, sulphonylurea;  $\alpha$ -GI,  $\alpha$ -glucosidase inhibitor; TZD, thiazolidinedione; DPP-4 I, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; SGLT2 I, Sodium-glucose cotransporter 2 inhibitor; ADA, anti-diabetes agents.

Table 1 – Characteristics of the included studies.

Subgroups	Number of studies	Heterogeneity test		Model selected	Mean difference	P-Value
		I <sup>2</sup>	P-Value			
HbA1c <7% (53 mmol/mol)						
Fasting glucose (mmol/L)	5	56%	0.06	Random	0.68 (0.39–0.97)	<0.00001
Postprandial glucose after breakfast (mmol/L)	5	53%	0.08	Random	0.67 (0.13–1.20)	0.01
Postprandial glucose after lunch (mmol/L)	4	75%	0.007	Random	-0.37 (-1.08–0.33)	0.30
Postprandial glucose after dinner (mmol/L)	5	81%	0.001	Random	-0.59 (-1.41–0.24)	0.16
Post-breakfast glucose spike (mmol/L)	4	67%	0.03	Random	-0.02 (-1.03–0.98)	0.96
HbA1c ≥7% (53 mmol/mol)						
Fasting glucose (mmol/L)	5	89%	<0.00001	Random	0.94 (0.37–1.50)	0.001
Pre-lunch glucose (mmol/L)	3	76%	0.01	Random	0.33 (-0.20–0.87)	0.23
Pre-dinner glucose (mmol/L)	3	94%	<0.00001	Random	0.28 (-0.67–1.23)	0.57
Postprandial glucose after breakfast (mmol/L)	4	83%	0.0005	Random	2.79 (1.88–3.70)	<0.00001
Postprandial glucose after lunch (mmol/L)	3	89%	0.0001	Random	1.60 (-0.11–3.31)	0.07
Postprandial glucose after dinner (mmol/L)	3	94%	<0.00001	Random	2.01 (-0.05–4.07)	0.06
Post-breakfast glucose spike (mmol/L)	3	74%	0.02	Random	2.29 (1.40–3.18)	<0.00001
Post-lunch glucose spike (mmol/L)	2	90%	0.002	Random	1.32 (-1.11–3.76)	0.29
Post-dinner glucose spike (mmol/L)	2	91%	0.0009	Random	1.87 (-1.06–4.79)	0.21
Duration of diabetes <10 years						
Fasting glucose (mmol/L)	5	89%	<0.00001	Random	1.06 (0.39–1.72)	0.002
Pre-lunch glucose (mmol/L)	3	72%	0.01	Random	0.33 (-0.20–0.87)	0.23
Pre-dinner glucose (mmol/L)	3	87%	0.0005	Random	0.40 (-0.37–1.18)	0.31
Postprandial glucose after breakfast (mmol/L)	4	79%	0.003	Random	1.37 (0.50–2.23)	0.002
Postprandial glucose after lunch (mmol/L)	3	92%	<0.00001	Random	0.90 (-0.92–2.73)	0.33
Postprandial glucose after dinner (mmol/L)	3	90%	<0.0001	Random	1.13 (-0.85–3.10)	0.26
Post-breakfast glucose spike (mmol/L)	3	62%	0.07	Random	1.26 (0.15–2.38)	0.03
Post-lunch glucose spike (mmol/L)	2	94%	<0.0001	Random	0.91 (-2.42–4.24)	0.59
Post-dinner glucose spike (mmol/L)	2	94%	<0.0001	Random	1.51 (-2.21–5.22)	0.43
Duration of diabetes ≥10 years						
Fasting glucose (mmol/L)	2	20%	0.26	Fixed	0.80 (0.45–1.15)	<0.00001
Postprandial glucose after breakfast (mmol/L)	3	92%	<0.00001	Random	2.22 (0.41–4.03)	0.02
Postprandial glucose after lunch (mmol/L)	2	85%	0.009	Random	0.87 (-1.48–3.22)	0.47
Postprandial glucose after dinner (mmol/L)	2	96%	<0.00001	Random	0.90 (-2.43–4.23)	0.60
Post-breakfast glucose spike (mmol/L)	2	95%	<0.00001	Random	1.04 (-2.68–4.77)	0.58

Dara are presented as mean difference (95% CI)

**Table 2 – Mean difference between fasting glucose, pre-meal glucose and postprandial glucose and the IDF targets (Fasting glucose ≤6.5 mmol/L, Pre-meal glucose ≤6.5 mmol/L, Postprandial glucose ≤9 mmol/L, Post-meal glucose spike ≤2.5 mmol/L): a subgroup analysis.**

## Figure Captions

**Fig. 1 – PRISMA diagram of the study selection process.**

**Fig. 2 – Forest plots of mean differences between (A) fasting glucose, (B) pre-lunch glucose and (C) pre-dinner glucose and the IDF targets (Fasting glucose  $\leq 6.5$  mmol/L, Pre-meal glucose  $\leq 6.5$  mmol/L): an overall analysis. Abbreviation: SE, standard error.**

**Fig. 3 – Forest plots of mean differences between (A) postprandial glucose after breakfast, (B) postprandial glucose after lunch, (C) postprandial glucose after dinner, (D) post-breakfast glucose spike, (E) post-lunch glucose spike and (F) post-dinner glucose spike and the IDF targets (Postprandial glucose  $\leq 9$  mmol/L, Post-meal glucose spike  $\leq 2.5$  mmol/L): an overall analysis. Abbreviation: PPG, postprandial glucose; SE, standard error.**



